PES

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 37/02 — A1

(11) International Publication Number: WO 94/28923

(43) International Publication Date: 22 December 1994 (22.12.94)

(21) International Application Number: PCT/US94/06418

(22) International Filing Date: 7 June 1994 (07.06.94)

(30) Priority Data:
08/075,032 10 June 1993 (10.06.93) US

(71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).

(72) Inventors: AOKI, K., Roger; 25472 Earhart Road, Laguna Hills, CA 92653 (US). GRAYSTON, Michael, W.; 12 Mandarin, Irvine, CA 92714 (US). CARLSON, Steven, R.; 29991 Happy Sparrow Lane, Laguna Niguel, CA 92677 (US). LEON, Judith, M.; 29992 Running Deer Lane, Laguna Niguel, CA 92677 (US).

(74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

AIM INFORMATION SERVICES
P.O. BOX 405, CORTE MADERA, CA 94976-0405
(415) 927-0340 • FAX (415) 927-7250

(54) Title: MULTIPLE BOTULINUM TOXINS FOR TREATING NEUROMUSCULAR DISORDERS AND CONDITIONS

(57) Abstract

A method and composition for treating a patient suffering from a disease, disorder or condition include the administration to the patient of a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G. The amount of each selected neurotoxin administered is further selected to control a duration of therapeutic activity of the administered combination.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

MULTIPLE BOTULINUM TOXINS FOR TREATING NEUROMUSCULAR DISORDERS AND CONDITIONS

FIELD OF THE INVENTION

The present invention provides novel methods and composition for treating diseases of the nervous system, e.g., neuromuscular disorders and conditions, with botulinum toxins. In addition, the present invention provides methods useful in all tissue and organ systems which involve the release of neurotransmitters, especially acetylcholine. These cholinergic transmission systems include neuromuscular junctions (muscles), smooth muscles (gut, sphincters, etc.) and secretions (salivation and mucus).

BACKGROUND OF THE INVENTION

A bacterial toxin, botulinum toxin, in particular botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscle afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

Botulinum toxin type A, the toxin type generally utilized in treating neuromuscular conditions, is currently available commercially from several sources; for example, from Port Products Ltd. UK, under the trade name "DYSPORT," and from Allergan, Inc., Irvine, California, under the trade name BOTOX®.

It is one object of the invention to provide novel treatments of neuromuscular disorders and conditions with botulinum toxin type A in combination with botulinum toxin types B, C, D, E, F and G.

SUMMARY OF THE INVENTION

The present invention provides a composition and a method of treating a neuromuscular disorder or condition such as strabismus and other disorders of ocular motility, e.g., comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, etc.; dystonia, e.g., focal dystonias such as spasmodic torticollis, writer's cramp, blepharospasm, oromandibular dystonia and the symptoms thereof, e.g., bruxism, Wilson's disease, tardive dystonia, laryngeal dystonia etc.; other dystonias, e.g., tremor, tics, segmental myoclonus; spasms, such as spasticity due to chronic multiple sclerosis, spasticity resulting in abnormal bladder control, e.g., in patients with spinal cord injury, animus, back spasm, charley horse etc.; tension headaches; levator pelvic syndrome; spina bifida, tardive dyskinesia; Parkinson's and limb (focal) dystonia and stuttering, etc. of a patient, which method comprises administering to the patient suffering from said disorder or condition a therapeutically effective amount of botulinum toxin

type A in combination with a neurotoxin selected from the group consisting of botulinum toxin types B, C, D, E, F and G. The clinical features of the above-listed neuromuscular disorders and conditions are described in Jankovic and Brin, cited above, and in Quinn, *Disorders of Movement*, Academic Press, 1989, all of which are incorporated herein by reference.

The present invention further provides compositions of said botulinum toxins in a vehicle suitable for injection of said toxins into the appropriate region of the patient to be treated. Alterations of the vehicle and excipient may include materials designed to retain the injected toxin in the local area.

The present invention further provides a composition and a method for treating neuromuscular disorders or conditions requiring a short duration of therapeutic action (measured in hours or days) or an intermediate duration of therapeutic action (measured in weeks). For example, a short or intermediate duration neurotoxin may be used in procedures to temporarily immobilize a joint or prevent muscle contractions prior to or after surgery or a procedure. Examples of these conditions include: total joint replacement, treatment of compound fractures, joint infections, dislocations. Other uses of a short duration of action product are to aid in joint dislocations, relaxation for physical therapy, alleviation of muscle spasms (to break the cycle of pain and spasm). In addition, a short duration therapy may be useful to determine the muscles involved in curvature of the spine in scoliosis. Unusual spasms of sphincter muscles (ocular,

gastrointestinal, vaginal, etc.) may be treated with short duration therapy.

On the other hand, an intermediate duration product may be useful in treating tendon or ligament alignment repair. If a muscle is damaged after trauma, immobilization with an intermediate may help with pain and facilitate healing. In addition, an intermediate duration therapy may be useful in determination of muscles involved in curvature of the spine in scoliosis. Unusual spasms of sphincter muscles (ocular, gastrointestinal, vaginal, etc.) may be treated with intermediate duration therapy.

DETAILED DESCRIPTION

The botulinum toxins used according to the present invention are botulinum toxins type A, B, C, D, E, F and G.

Each serotype of botulinum toxin has been identified as immunologically different proteins through the sue of specific antibodies. For example, if the antibody (antitoxin) recognizes, that is, neutralizes the biological activity of, for example, type A it will not recognize types B, C, D, E, F or G.

While all of the botulinum toxins appear to be zinc endopeptidases, the mechanism of action of different serotypes, for example, A and E within the neuron appear to be different than that of type B. In addition, the neuronal surface "receptor" for the toxin appears to be different for the serotypes.

The physiologic groups of *Clostridium botulinum* types are listed in Table I.

Table I. Physiologic Groups of *Clostridium botulinum*

Group	Toxin Sero-Type	Biochemistry	Milk Digest	Glucose Fermentation	Lipase	Phages & Plasmids	Phenotypically Related Clostridium (nontoxigenic)
I	A,B,F	proteolytic saccharolytic	+	+	+	+	C. sporogenes
II	B,E,F	nonproteolytic saccharolytic psychotrophic	-	+	+	+	
III	C,D	nonproteolytic saccharolytic	+	+	+	+	C. novyi
IV	G	proteolytic nonsaccharolytic	+	-	-	-	C. subterminale

These toxin types may be produced by selection from the appropriate physiologic group of *Clostridium botulinum* organisms. the organisms designated as Group I are usually referred to as proteolytic and produce botulinum toxins of types A, B and F. The organisms designated as Group II are saccharolytic and produce botulinum toxins of types B, E and F. The organisms designated as Group III produce only botulinum toxin types C and D and are distinguished from organisms of Groups I and II by the production of significant amounts of propionic acid. Group IV organisms only produce neurotoxin of type G. The production of any and all of the botulinum toxin types A, B, C, D, E, F and G are described in Chapter 1 of *Botulinum Neurotoxin and Tetanus Toxin*, cited above, and/or the references cited therein. Botulinum toxins types B, C, D, E, F and G are also available from various species of clostridia. Currently fourteen species of clostridia are considered pathogenic. Most of the pathogenic strains produce toxins which are responsible for the various pathological signs and symptoms. Organisms which produce botulinum toxins have been isolated from botulism outbreaks in humans

(types A, B, E and F) and animals (types C and D). Their identities were described through the use of specific antitoxins (antibodies) developed against the earlier toxins. Type G toxin was found in soil and has low toxigenicity. However, it has been isolated from autopsy specimens, but thus far there has not been adequate evidence that type G botulism has occurred in humans.

In general, four physiologic groups of *C. botulinum* are recognized (I, II, III, IV). The organisms capable of producing a serologically distinct toxin may come from more than one physiological group. For example, Type B and F toxins can be produced by strains from Group I or II. In addition, other strains of clostridial species (*C. baratii*, type F; *C. butyricum*, type E; *C. novyi*, type C_1 or D) have been identified which can produce botulinum neurotoxins.

Preferably, the toxin is administered by means of intramuscular injection directly into a spastic muscle, in the region of the neuromuscular junction, although alternative types of administration (e.g., subcutaneous injection), which can deliver the toxin directly to the affected muscle region, may be employed where appropriate. The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by

means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is unpreserved.

It is preferred that the toxin is formulated in unit dosage form; for example, it can be provided as a sterile solution in a vial or as a vial or sachet containing a lyophilized powder for reconstituting a suitable vehicle such as water for injection.

In one embodiment, the botulinum toxin is formulated in a solution containing saline and pasteurized human serum albumin, which stabilizes the toxin and minimizes loss through non-specific adsorption. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum-dried to give a sterile lyophilized powder. In use, the powder can be reconstituted by the addition of sterile unpreserved normal saline (sodium chloride 0.9% for injection).

The dose of toxin administered to the patient will depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin. The potency of the toxin is expressed as a multiple of the LD_{50} value for the mouse, one unit (U) of toxin being defined as being the equivalent amount of toxin that kills 50% of a group of 18 to 20 female Swiss-Webster mice, weighing about 20 grams each.

The dosages used in human therapeutic applications are roughly proportional to the mass of muscle being injected. Typically, the dose administered to the patient may be up to about 1,000 units;

for example, up to about 500 units, and preferably in the range from about 80 to about 460 units per patient per treatment, although smaller of larger doses may be administered in appropriate circumstances.

As the physicians become more familiar with the use of this product, the dose may be changed. In the botulinum toxin type A, available from Porton, DYSPORT, 1 nanogram (ng) contains 40 U. 1 ng of the botulinum toxin type A, available from Allergan, Inc., i.e., BOTOX®, contains 4 U. The potency of botulinum toxin and its long duration of action mean that doses will tend to be administered on an infrequent basis. Ultimately, however, both the quantity of toxin administered and the frequency of its administration will be at the discretion of the physician responsible for the treatment and will be commensurate with questions of safety and the effects produced by the toxin.

The invention will now be illustrated by reference to the following nonlimiting examples.

In each of the examples, the appropriate muscles of each patient are injected with a sterile solution containing the confirmation of botulinum toxin. Total patient doses range from 80 U to 460 U. Before injecting any muscle group, careful consideration is given to the anatomy of the muscle group, the aim being to inject the area with the highest concentration of neuromuscular junctions , if known. Before injecting the muscle, the position of the needle in the muscle is confirmed by putting the muscle through its range of motion and observing the resultant motion of the needle end. General

anaesthesia, local anaesthesia and sedation are used according to the age of the patient, the number of sites to be injected, and the particular needs of the patient. More than one injection and/or sites of injection may be necessary to achieve the desired result. Also, some injections, depending on the muscle to be injected, may require the use of fine, hollow, teflon-coated needles, guided by electromyography.

Following injection, it is noted that there are no systemic or local side effects and none of the patients are found to develop extensive local hypotonicity. The majority of patients show an improvement in function both subjectively and when measured objectively.

Example 1
The Use of Botulinum Toxin Type in the Treatment of Tardive Dyskinesia

A patient, suffering from joint dislocation, is treated with a composition having up to 500 units of botulinum toxin type A and a lesser amount of botulinum toxin type B by direct injection of such toxin into the joint. After several hours, the joint is immobilized and muscle contractions are relieved. An increase, or enhancement, of the relief of muscle enhancement caused by the combination of botulinum toxin type A and B for a short duration enables immediate treatment while the long term relief of muscle enhancement enables healing of the reset joint.

Example 1(a)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and B is used with similar results.

Example 1(b)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and C is used with similar results.

Example 1(c)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and D is used with similar results.

Example 1(d)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and E is used with similar results.

Example 1(e)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and F is used with similar results.

Example 1(f)

The method of Example 1 is repeated, except that a combination of botulinum toxin type A and G is used with similar results.

Example 2
Use of Botulinum Toxin in the Treatment of Spasmodic Torticollis

A patient, suffering from spasmodic torticollis, as manifested by spasmodic or tonic contractions of the neck musculature, producing stereotyped abnormal deviations of the head, the chin being rotated to one side, and the shoulder being elevated toward the side at which the head is rotated, is treated by injection with a composition having up to 300 units, or more, of botulinum toxin type A and up to 300 units, or more, of botulinum toxin type E, in the dystonic neck muscles. After a few hours, the symptoms are substantially alleviated; i.e., the patient is able to hold his head and shoulder in a normal position.

Example 3
Use of Botulinum Toxin in the Treatment of Essential Tremor

A patient suffering from essential tremor, which is provoked by maintenance of posture or movement, is treated by injection with therapeutic amounts of botulinum toxin type A and botulinum toxin type B. After two weeks, the symptoms are substantially alleviated.

Example 3(a)

The method of Example 3 is repeated except that a patient suffering from essential tremor is injected with botulinum toxin type A and C. A similar result is obtained.

Example 3(b)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with botulinum toxin type A and D. A similar result is obtained.

Example 3(c)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with botulinum toxin type A and E. A similar result is obtained.

Example 3(d)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with botulinum toxin type A and F. A similar result is obtained.

Example 3(e)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with botulinum toxin type A and G. A similar result is obtained.

Example 4
Use of Botulinum Toxin in the Treatment of Spasmodic Dysphonia

A patient, unable to speak clearly due to spasm of the vocal chords, is treated by injection of therapeutic amounts of botulinum toxin type A and therapeutic amounts of botulinum toxin type B. After a few hours, the patient is able to speak clearly.

Example 4(a)

The method of Example 4 is repeated except that a patient suffering from spasmodic dysphonia is injected with botulinum toxin type A and C. A similar result is obtained.

Example 4(b)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with botulinum toxin type A and D. A similar result is obtained.

Example 4(c)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with botulinum toxin type A and E. A similar result is obtained.

Example 4(d)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is

injected with botulinum toxin type A and F. A similar result is obtained.

Example 4(e)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with botulinum toxin type A and G. A similar result is obtained.

Example 5
Use of Botulinum Toxin in the Treatment of Hemifacial Spasm

A patient is suffering from hemifacial spasm as manifested by involuntary rapid synchronous contraction of muscles innervated by the facial nerve on one side. The symptoms are sufficiently advanced to show not only contraction of the muscles around the eye, but twitches spread to involve the other ipsilateral facial muscles. The patient is injected with up to 300 units of botulinum toxin type A and up to 300 units of botulinum toxin type B, and after a few hours, the symptoms are substantially alleviated.

Example 5(a)

The method of Example 5 is repeated except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and C. A similar result is obtained.

Example 5(b)

The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and D. A similar result is obtained.

Example 5(c)

The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and E. A similar result is obtained.

Example 5(d)

The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and F. A similar result is obtained.

Example 5(e)

The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and G. A similar result is obtained.

Example 6

Use of Botulinum Toxin in the Treatment of Blepharospasm

A 60-year old woman suffering from idiopathic blepharospasm, a focal form of dystonia involving the orbicularis oculi muscles and producing involuntary

eye closure, is treated by injection with a therapeutic amount of botulinum toxin type A and type B into the orbicularis oculi muscle. A total of eight injections, both laterally and medially at the junction of the orbital and preseptal orbicularis is made. Twice as much of the solution is injected laterally as medially. Within twelve to twenty-four hours, detectable muscle weakness begins. Clinical improvement shows in two to three days. The involuntary blinking ceases. The effect of the injections lasts for 75 days.

Example 6(a)

The method of Example 6 is repeated except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and C. A similar result is obtained.

Example 6(b)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and D. A similar result is obtained.

Example 6(c)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and E. A similar result is obtained.

Example 6(d)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and F. A similar result is obtained.

Example 6(e)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and G. A similar result is obtained.

Although there has been hereinabove described a use of multiple botulinum toxins for treating neuromuscular disorders and conditions in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto since many obvious modifications can be made, and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being further selected to control a duration of therapeutic activity of the administered combination.

2. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and B.

3. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and C.

4. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and D.

5. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and E.

6. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and F.

7. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and G.

8. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevent of muscle contractions prior to or after surgery.

9. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

10. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of botulinum toxin type A and after a period of time administering to the patient a therapeutically effective amount of at least one neurotoxin selected from a group consisting of botulinum toxin types B, C, D, E, F and G in order to provide a short term enhancement of the therapeutic effect of the botulinum toxins.

11. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type B.

12. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type C.

13. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type D.

14. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type E.

15. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type F.

16. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type G.

17. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being further selected to control a duration of therapeutic activity of the administered combination.

18. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and B.

19. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and C.

20. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and D.

21. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and E.

22. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and F.

23. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and G.

24. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevent of muscle contractions prior to or after surgery.

25. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/US 94/06418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 05800 (ALLERGAN) 1 April 1993 see the whole document, specially page 12, par. 4	1-25
X	MICROBIOLOGICAL REVIEW, vol.56, no.1, March 1992, WASHINGTON, DC pages 80 - 99 SCHANTZ ET AL. 'Properties and Use of Botulinum Toxin and Other Microbial Neurotoxins in Medicine' see the whole document and specially page 93, right column	1-25

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1994	18. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF NEUROLOGY, vol.239, no.1, January 1992, BERLIN pages 16 - 20 HAMBLETON P. 'Clostridium botulinums toxins: a general review ...' see the whole document	1-25
A	THE NEW ENGLAND JOURNAL OF MEDICINE, vol.324, no.17, 25 April 1991, BOSTON pages 1186 - 1194 JANKOVIC J. ET AL. 'Therapeutic Uses of Botulinum Toxin' cited in the application see the whole document	1-25
P,X	WO,A,94 00481 (ASSOCIATED SYNAPSE BIOLOGICS) 6 January 1994 see the whole document	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06418

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERN. ..IONAL SEARCH REPORT

Information on patent family members

Inten ..nal Application No
PCT/US 94/06418

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9305800	01-04-93	AU-A-	2566492	27-04-93
		CA-A-	2119562	01-04-93
		EP-A-	0605501	13-07-94
WO-A-9400481	06-01-94	AU-B-	4646393	24-01-94